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Editorial

Commentary and debate

Adolescent tuberculosis

One of the most intriguing features of the epidemiology of tuberculosis is the well-known variation in the age incidence of disease and the variation in the nature of the disease with age.

During infancy and early childhood, tuberculous disease is particularly liable to follow infection and high morbidity and mortality are experienced.[1] Disseminated forms of disease, such as miliary tuberculosis and tuberculous meningitis, are particularly likely to develop. Respiratory tuberculosis in young children is mainly related to the primary complex and the progression of one or more of its components. Cavitation can occur in young children, but is unusual.[2]

Between the ages of about 5 and 10 years, children enter a period of relative protection from tuberculous disease, despite a persistent risk of infection as evidenced by an uninterrupted rise in the proportion of children with a positive tuberculin test. In South Africa, between 1970 and 1980, the tuberculosis case fatality rate was 7% for children < 1 year of age falling to 3% for those 1 - 4 years and 1% for those 5 - 9 years.[3] After the age of 10 years, however, an ever-increasing risk of tuberculous disease is experienced and the nature of the disease changes from primary to adult-type tuberculosis.[4] In South Africa there is a threefold increase in the risk of developing tuberculosis as children pass through adolescence to young adulthood. In the Western Cape this risk is increased sixfold.[5] Disease in adolescence becomes characteristically that of adult-type pulmonary tuberculosis, also called chronic pulmonary tuberculosis, post-primary or secondary tuberculosis. Respiratory disease now involves mainly the apices of the lungs, and cavitation becomes an integral part of the disease process, contributing not only to the destruction of lung tissue, but also to the spread of infection in the community.

An equally curious feature of tuberculosis in adolescence is the female predominance, which is most obvious under epidemic conditions.[6] The risk of developing adult-type pulmonary tuberculosis in adolescence is 2 - 6 times greater in females than males and its occurrence is frequently associated with menarche.[7-9] Notwithstanding this female predilection for the development of pulmonary tuberculosis, rates of infection as evinced by a positive tuberculin test are usually similar for males and females and even show a male predominance in many studies.[10] Despite this well-documented female predominance in adolescent pulmonary tuberculosis, tuberculous pleural effusions in adolescence show a male predominance.[11]

The above epidemiological characteristics of tuberculosis were well known to earlier generations of researchers, but have been neglected in recent years. Explanations advanced generally drew upon a vague hormonal or endocrinological explanation compounded by the metabolic perturbations of puberty.[4,6,7] Arvid Wallgren therefore stated: 'It is quite likely that the liability to pulmonary tuberculosis (in adolescence) is intimately linked up with endocrine activity. In this way may also the decreased resistance during pregnancy be explained . . ..'[4] Margaret Smith commented: 'The depressing effect of puberty in the girl on the retention of nitrogen and calcium . . . may be determining factors in the higher rate of chronic pulmonary tuberculosis in young adolescent females.'[7]

In discussing the potential importance of the factors involved in this phenomenon, Arnold Rich wrote: 'The most earnest study should be devoted to an elucidation of the factors which influence the development of progressive tuberculosis at this time of life, for the precise reasons for the disastrous effects observed during this period, and later in life as a result of infection occurring during this period, are still for the most part obscure and the problem is one not only of extraordinary theoretical interest, but of the utmost importance from the standpoint of human welfare.'[12]

Recent developments in our understanding of hormonal influences upon the immune system have begun to offer more precise hypotheses for these facts. It now seems possible that an endocrinological effect upon the capacity of the immune system to control stationary-phase dormant tuberculosis bacilli contributes to adolescent susceptibility to disease and affects the nature of the disease process.[13]

Two types of tissue response to the intradermal injection of tuberculin in an individual previously infected with *Mycobacterium tuberculosis* can be identified. Firstly, there is a non-necrotising response which correlates with immunity and secondly, a necrotising response, as in the well-known Koch phenomenon, which does not correlate closely with protection.[14] Similarly, two subsets of helper T cells, Th1 and Th2, have been identified, with distinct profiles of cytokine secretion.[15] *In vivo*, acting in concert with other cell types, these give rise to two patterns of cytokine release known as type 1 (IL-2, IL-12, and gamma-interferon) and type 2 (IL-4, 5, 6, 10 and 13). The balance of the two 'families' of cytokines may be critical in determining resistance or progression of HIV infection to AIDS.[16] This balance may be equally important in other chronic infections such as tuberculosis.[13] Indeed, evidence from *in vivo* cytokine neutralisation experiments and gene knockout mice supports the view that the type 1 response, which stimulates cell-mediated immunity, is also needed (J. Flynn and B. R. Bloom — personal communication), probably as an additional activator of macrophages. Paradoxically, however, there are also strong arguments for the view that tumour necrosis factor alpha (TNFα) is responsible for some of the necrosis and weight loss in tuberculosis,[17] and the recent observation that administration of thalidomide causes weight gain and symptomatic relief in tuberculosis patients lends support to this concept (G. Kaplan — personal communication), because thalidomide decreases production of TNFα. The paradox may be resolved by the observation that whereas TNFα is non-toxic when injected into a relatively 'pure' type 1 inflammatory site, where it

presumably contributes to macrophage activation, it causes necrosis when injected into a mixed type 1 + type 2 site.[18] This may explain the dual role of TNFα in tuberculosis, because patients show a clear type 1-to-type 2 shift. For instance the IL-4 gene is expressed in patients' peripheral blood T cells[19,20] and there is IgE antibody, which is dependent on IL-4.[21]

The balance of type 1-to-type 2 activity appears to be regulated by adrenal steroids, so it is logical to seek explanations for adolescent tuberculosis in the striking changes in adrenal function that occur at puberty. At all ages, the release of IL-1, IL-6 and TNFα from sites of immunological activity activates the hypothalamic pituitary adrenal axis and increases glucocorticoid production.[22] Glucocorticoids for their part inhibit Th1 activity and synergise with IL-4, and thus create a bias towards Th2 activity.[23] In contrast to the glucocorticoids, the adrenal androgen dehydroepiandrosterone (DHEA), or perhaps a metabolite of DHEA formed *in vivo*,[24] acts as a genuine anti-glucocorticoid[25] and also promotes a Th1 response.[26] In tuberculosis and HIV infection a decrease in the DHEA/cortisol ratio is well documented and in HIV infection is associated with progression to AIDS.[13,27]

One would therefore anticipate that a high DHEA/cortisol ratio would favour a protective type 1 response. However, what we know of childhood tuberculosis suggests the reverse correlation. DHEA levels are high during the first year of life when the risk of disease and mortality from tuberculosis is highest. DHEA levels remain low from 1 year until about 8 years of age, during which time the risk of disease is also decreasing although the risk of infection remains constant. The rise in the incidence of tuberculous disease during adolescence correlates with a rise in DHEA levels. DHEA secretion throughout childhood and adolescence is higher in girls than in boys,[28,29] correlating with a greater risk of disease in girls in this age group. Cortisol secretion, however, apart from its diurnal variation, remains constant during adolescence.

These points lead to some difficult but important questions. First, what is the mechanism of immunity to tuberculosis in children from 1 to 8 years? Is it a type 1 response? If so, why does it function so well without DHEA? Is a relevant downstream metabolite of DHEA produced via a different route in the prepubertal adrenal? The truth is that we do not know the final effector mechanism even for the adult response, since human macrophages have not been convincingly shown to kill *M. tuberculosis*, and we know nothing at all about the mechanisms present in children. This question clearly deserves investigation.

Secondly, does the increase in DHEA at puberty convert the response to an adult type? If so why does it fail so often, leading to adult-type cavitatory disease rather than adult-type immunity? Perhaps the failure is an effect of other hormones that appear at the same time. For instance, there is some evidence that dihydrotestosterone can downregulate production of gamma interferon.[30]

A further hormonal factor which may operate during the period of rapid bone growth in adolescence, and which may influence the Th1/Th2 balance, is the immunoregulatory role of vitamin D and its metabolites, which function independently of the control by parathyroid hormone. Autocrine conversion of 25-OHD_3 to active $1,25(OH)_2D_3$ (calcitriol) by interferon gamma-activated macrophages appears to be essential for immunity to tuberculosis.[31] The production of $1,25(OH)_2D_3$ may however be a double-edged sword as excessive amounts may promote a Th2-type response with the release of TNFα and tissue necrosis.[18,32] There are few published data on the production of $1,25(OH)_2D_3$ during adolescence, but it is not unlikely that a surfeit generated by active bone metabolism during this period of life may affect immunity to tuberculosis.

As our understanding of the factors promoting tissue necrosis increases so does the possibility of influencing this process. As it is tissue necrosis and cavitation that promote the expectoration of large numbers of *M. tuberculosis* during coughing, the epidemiological implications of understanding and controlling the process are considerable. Study of the neuro-endocrinological influences operating in HIV infection and AIDS has already advanced our understanding of the functioning of the immune system during chronic disease processes. The application of similar methodologies in adolescent tuberculosis may prove equally rewarding.

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OPINION

Compensation for disabilities

Determining just compensation for disabilities is difficult even when assessment is by competent and experienced professionals.

There is much that is unsatisfactory in the mechanisms for awarding compensation in South Africa. As in other countries which have inherited aspects of English law, the system in South Africa is adversarial: the court cannot make judgements unless the facts are presented by opposing parties. Controversy is necessary to allow the courts to hear the matter. The system creates adversaries, even where none should exist, so that what should be a dispassionate judgement of disability becomes a contest of strength.

Separate court systems exist for liquor licensing, income tax, industrial relations, workmen's compensation and water affairs because these fields have specialised complexity, but it is the general courts which pass judgement on subtle and intricate medical issues — almost always without the benefit of a medical expert sitting with the judge.

A further complication is that the medical aspect (which entails the quantification of disability, comprising about 80% of the case) and the legal aspect (determining fault) tend to fuse. As a result, the medical profession's role in quantifying disability has largely yielded to the lawyer's adversarial determinations.

The medical assessor, who would be an appropriate and effective executive authority in assessing disability, has been replaced in the adversarial system by the medical witness who plays little more than a subservient role — instructed, recruited or excluded as it best serves the lawyer. The medical witness is often drawn into the proceedings by chance, civic duty or innocent helpfulness. He is thrust into an adversarial interchange with which he is unaccustomed and placed under stress in the unfamiliar territory of a court of law. At times he is unpleasantly harried by cross-examination when legal techniques are used in attempts to discredit or unsettle his medical judgements. He is then expected to be objectively and articulately instructive toward lawyer, advocate and judge in matters medical.

After this, lawyer and judge claim to have acquired a knowledge of the science, experience, interpretive subtleties and intuitions necessary to make medical judgements. Not surprisingly misapprehensions occur, and when court judgements are appraised from a medical point of view, inappropriate awards seem to occur frequently.

As a result of the abovementioned factors, and perhaps others, many medical people are reluctant to appear on behalf of the injured party.

A number of factors further militate against just awards of compensation: these include population ignorance, lawyer workload or lawyer inexperience, fraud and the costs and financial risks of Supreme Court action. If, in addition, the claimant has difficulty in obtaining sincere medical witnesses of an appropriate calibre to support his claim, the current process of claiming compensation may well degenerate. The outcome could be an increase in fraudulent claims, contingency litigation (percentage of award to lawyer) and the use of 'hired gun' medical witnesses.

I believe that, under the present system, there is a grave danger that the disincentives to make claims for disabilities could become so great as to jeopardise just compensation of the disabled.

It is the medical profession's responsibility to close this unsatisfactory gap in the health sciences and to reclaim the role of impartial assessors of disability and compensation — with appropriate legal assistance (rather than legal control). The realist will recognise that it is far easier to familiarise a medical expert with the adjunctive areas of law — which are fairly consistent — than it is for a medical expert repetitively to instruct a court on matters medical, a different (and expensive) exercise with each different injury and each different case.

The appropriate route for the medical profession could be via techniques of dispute mediation or arbitration. 'No fault' compensation has many commendable advantages and strong support from the medical profession will be necessary for the concept to gain ground.

To improve the accuracy and expedition of disability compensation the medical profession needs to address the training of medical personnel as assessors of disability. The skills and science of appraising handicap require development along with awareness of the monetary and impedimentary value of the losses caused by disablement. These needs would best be served by the establishment of an institute for the measurement of disability, where objective methods of measuring disability could be researched, developed and taught, and disability appraised by skilled, eclectic professionals. Support from the insurance industry would more than pay for itself and benefit that industry and society as a whole.

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